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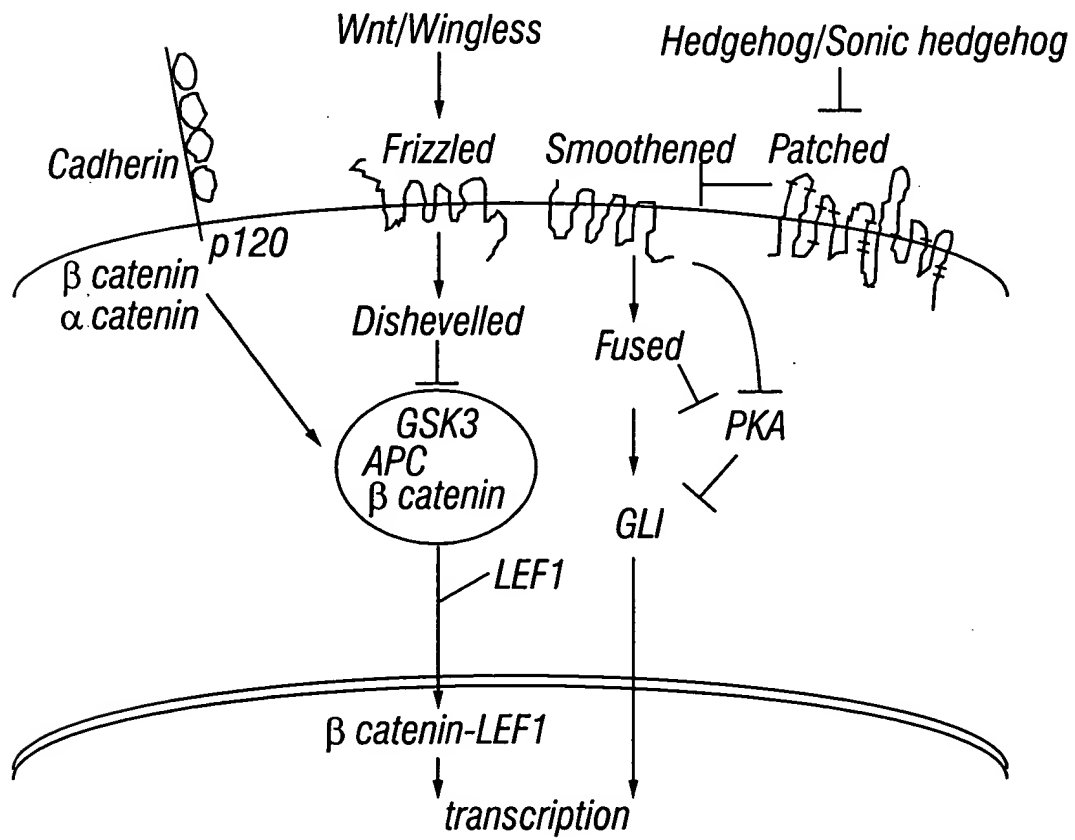


FIG. 1

## Alignment of several frizzled family members

fz3/mouse -----MAVSWIVFDLWLLTVFLG---QIGGHS-----LFSCE.  
fz4/mouse -----MAWPGTGPS---SRGAPGGVGLRLGLLLQFLLLLRPTLGFGD-----EEERRCD  
fz8/mouse -----MEWGYL-----LEVTSLLAALAVLQRSSG-AAAASAK-----ELACQ  
fz5/human -----MARPDP-----SAPPSLL--LLLLAQLVG-RAAAASK-----APVCQ  
fzd9/human -----MAVAPLRGALLWQLLAAGGAAL EIGRFD-----PERGRG-----AAPCQ  
fz1/rat LEAPLLLGVRAPAG---QVSG-PGQQRPPPPQPQQGG--QQYNGERG--ISIPDHGYCQ  
fz2/rat -----MRARSAL---PRSALPRLLLPLLLLPAAGP--AQFHGEKG--ISIPDHGFCQ  
fz/Dros ILPTLIQGVQRYDQS---PLDASPYRSGGGLMASSG---TELDG-----LPHHNRCE  
fz2/Dros/ GLVLLLTSCRADGPL-----HSADHGMGGMGMGGHGLD-ASPAPGYGVP AIPKDPNLRCE

\* ●

fz3/mouse	PITLRMCQDLPYNTTFMPNLLNHYDQQTAALAMEPFHMPVNLDCSRDFRPFLCALYAPIC
fz4/mouse	PIRIAMCQNLGYNVTKMPNLVGHELQTD AELQLTFTTPLIQYGCSSQLQFFLCSVYVPMC
fz8/mouse	EITVPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQCSDDLKFFLCSMYTPIC
fz5/human	EITVPMCRGIGYNLTHMPNQFNHDTQDEAGLEVHQFWPLVEIQCSDDLRFLLCTMYTPIC
fzd9/human	AVEIPMCRGIGYNLTRMPNLLGHTSQGEAAAEALAEFAPLVQYGCCHSLRFFLCSLYAPMC
fz1/rat	PISIPLECTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVC
fz2/rat	PISIPLECTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFLLCSMYAPVC
fz/Dros	PITISICKNIPYNMTIMPNLIGHTKQEEAGLEVHQFAPLVKIGCSDDLQLFLCSLYVPVC
fz2/Dros/	EITIPMCRGIGYNMTSFPNEMNHETQDEAGLEVHQFWPLVEIKCSDDLKFFLCSMYTPIC
	: : * : ** : ** * * * : : *:: * : : ** : **

fz3/mouse	M-EYGRVTLPCRRLCQRAYSECSKLMEMFG-VPWPEDMECSRFPDCD-EPYPRLVDLN--
fz4/mouse	TEKINIPIGPCGGMCLSVKRRCEPVLREFG-FAWPDTLNCSKFPPQN-DHNHMCMEGP--
fz8/mouse	LEDYKKPLPPCRSVCERAKAGCAPLMRQYG-FAWPDRMRCDLRLEQG-NPDTLCMDYN-R
fz5/human	LPDYHKPLPPCRSVCERAKAGCSPLMRQYG-FAWPERMSCDRLPVLGRDAEVL CMDYN-R
fzd9/human	TDQVSTPI PACRPMCEQARLRCAPI MEQFN-FGWPDSLDCARLPTRN-DPHALCMEAPEN
fz1/rat	T-VLEQALPPCRSLCERA-QGCEALMNKFG-FQWPDTLKCEKFPVHG--AGELCVGQNTS
fz2/rat	T-VLEQAIPPCR SICERARQGCEALMNKFG-FQWPERLRCEHFPRHG--AEQICVGQNHS
fz/Dros	T-ILERPIPPCRSLCESA-RVCEKLMKTYN-FNWPENLECSKFVPVHG--GEDLCVAENTT
fz2/Dros/	LEDYHKPLPVCRSVCERARSGCAPIMQQYS-FEWPERMACEHLPLHG-DPDNLCMEQPSY
	*   *   *                      **   .   *   .   *

**FIG. 2A**

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fz3/mouse -----LVGDPT-----
fz4/mouse ---GDE-----VPLPHKTP-
fz8/mouse TDLTTAAPSPRRLLLLPPPPPPGEQPPSGSGHSRPPGARPPHRGGSSRGSGDAAAAPPSSRG
fz5/human SEATTAPPRP---FPAKP---TLP--G----PP-----G---APAS-GG
fzd9/human ATAGPAEPHK---GLGM---LP-----VAPRPAPPPG
fzl/rat   DKGTPTPSL-----L-----PEFWTSNPQHG
fz2/rat   EDG--TPAL-----L-----TTAPPSGLQPG
fz/Dros   SSA-----STAATPTRSVA
fz2/Dros/ TEAGSGGSSG---GSGG---SGSGSGSGGKRKQGGSGSGGAGGSSGSTSTKPCR-GR
amino terminal domain continued

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                                     TM1
fz3/mouse  YSFLHVRDCSPPCPN-----MYFRREELSFARYFIGLISIICLSATLFTFLTLIDVTR
fz4/mouse  --LNCVLKCGYDAG-----LYSRSAKEFTDIWMAVWASLCFISTTFTVLTLIDSSR
fz8/mouse  -KTGQIANCALPCHN-----PFFSQDERAFTVFWIGLWSVLCFVSTFATVSTFLIDMER
fz5/human  -RTGQVPNCAVPCYQ-----PSFSADERTFATFWIGLWSVLCFISTSTTVATFLIDMDT
fzd9/human --RSCAPRCGPGVEV-----FWSRRDKDFALVWMAVWSALCFFSTAFTVLTLLEPHR
fzl/rat    LG EK---DCGAPCEPTKVYGLMYFGPEELRFSRTWIGIWSVLCCASTLFTVLTYLVDMMR
fz2/rat    LG ER---DCAAPCEPARPDGSMFFSHHHTRFARLWILTWSVLCCASTFTVTTSIVAMQR
fz/Dros    VGGKDLHDGAPCH-----AMFFPERERTVLRVWGSWAACVASCFTVLTLTLIDSSR
fz2/Dros/  QRIAGVPNCGIPCKG-----PFFSNDEKDFAGLWIALWSGLCFCSTLMTLTFTIIDTER
          *                               :  :  *           :.  *

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                                     TM2  extracellular domain loop 1
fz3/mouse  FRYPERPIIFYAVCYMMVSLIFFIGFLE-DRVACNASSP-----
fz4/mouse  FSYPERPIIFLSMCYNIYSIAYIVRLTVGRERISCDF-----
fz8/mouse  FKYPERPIIFLSACYLFVSVGYLVRLVAGHEKVACSGGAPGAGGRGGAGGAAAAGAGAAG
fz5/human  FRYPERPIIFLSACYLCVSLGFLVRLVVGHASVACS-----
fzd9/human FQYPERPIIFLSMCYNVYSLAFLIRAVAGAQSVACD-----
fzl/rat    FSYPERPIIFLSGCTAVAVAYIAGFLE-DRVVCNDKFAE-----
fz2/rat    FRYPERPIIFLSGCTMVSVAYIAGFVLQ-ERVVCNERFSE-----
fz/Dros    FRYPERAIVFLAVCYLVVGACAYVAGLGAG-DSVSCREPPPPVK---LG-----
fz2/Dros/  FKYPERPIVFLSACYFMVAVGYLSRNLQNEEIACDG-----
* ****.::* . ** . :.

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FIG. 2B

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TM3  
fz3/mouse -----AQYKASTVTQGSNKA-<sup>←</sup>ACTMLFMVLYFFTMAGSVWVILTITWFLA  
fz4/mouse -----EAAEPVLIQEGKNTGCAIFLLMYFFGMASSIWWVILTITWFLA  
fz8/mouse RGASSPGARGEYEEELGAVEQHVRVETTPALCTVVFLLYFFGMASSIWWVILSLTWFLA  
fz5/human R-----EHNHIHYETTPALCTIVFLLVYFFGMASSIWWVILSLTWFLA  
fzd9/human -----QEAGALYVIQEGLENTGCTLVFLLLYFFGMASLLWVVLTLTWFLA  
fzl/rat -----DGARTVAQGTKKE-GCTILFMVLYFFSMASSIWWVILSLTWFLA  
fz2/rat -----DCYRTVQGGTKKE-GCTILFMVLYFFSMASSIWWVILSLTWFLA  
fz/Dros -----RLQMMSTITQGHROTTSCTVLFMALYFCCMAAFWWSCLAFAWFLA  
fz2/Dros/ -----LLLRESSTGPHSCTLVFLLTYFFGMASSIWWVILTFWFLA  
: \* :: : ... \*\* ::: :\*:

TM4 → extracellular domain loop 2 ←  
fz3/mouse AVPKWGSEAIKALLFHASAWGIPGTLTITILLAMNKIEGDNISGVCVGLYDVALRYF  
fz4/mouse AGLKWGHEAIEHSSYFHIAAWAIPAVKTIVILIMRLVDADELTGLCYVGNQNLDAITGF  
fz8/mouse AGMKWGNEAIAIGYSQYFHLAAWLVPSVKSIAVLALSSVDGDPVAGICYVGNQSLDNLRGF  
fz5/human AAMKWGNEAIAIGYQYFHLAAWLIPSVKSITALALSSVDGDPVAGICYVGNQNLNLSLRRF  
fzd9/human AGKKWGHEAIEAHGSYFHMAAWGLPALKTIVILTLRKVAGDELTGLCYVASTDAAALTGF  
fzl/rat AGMKWGHEAIEANSQYFHLAAWAVPAIKTITILALGQVDGDLVSGVCVGLNNVDALRGF  
fz2/rat AGMKWGHEAIEANSQYFHLAAWAVPAVKTITILAMQIDGDLVSGVCVGLNRLDPLRGF  
fz/Dros AGLKWGHEAIEHNSHLFHLVAVWVPAQTISVLALAKVEGDILSGVCVFGQLDTHSLGAF  
fz2/Dros/ AGLKWGNEAITKHSQYFHLAAWLIPTVQSVAVLLLSAVDGDPIGICYVGNLNPDLKTF  
: \*\*: \*: . \*\* \*\* \* .: \* : : .: \*:\*. \*

TM5  
fz3/mouse VLAPLCYVVVGVSLLLAGITISLNRVRIEIPLEKE-----NQDKLVKFMIRIGVFSILYL  
fz4/mouse VVAPLFTYLVIGTLFIAAGLVALFKIRSNLQK-DG----TKTDKLERLMVKIGVFSVLYT  
fz8/mouse VLAPLVIYLFITMFLLAGFVSLFRIRSVIKQGGP---TKTHKLEKLMIRLGLFTVLYT  
fz5/human VLGPLVLYLLVGTFLFLLAGFVSLFRIRSVIKQ-GG----TKTDKLEKLMIRIGIFTLLYT  
fzd9/human VLVPLSGYLVLGSSFLTGFVALFHIRKIMKT-GG----TNTEKLEKLMVKIGVFSILYT  
fzl/rat VLAPLFVYLFIGTSFLLAGFVSLFRIRTIMKH-DG----TKTEKLEKLMVRIGVFSVLYT  
fz2/rat VLAPLFVYLFIGTSFLLAGFVSLFRIRTIMKH-DG----TKTEPLERLMVRIGVFSVLYT  
fz/Dros LILPLCIYLSIGALFLLAGFISLFRIRTVMMKT-DG----KRTDKLERLMVRIGFFSGLFI  
fz2/Dros/ VLAPLFVYLVIGTTFLLMAGFVSLFRIRSVIKQGGVGAGVKADKLEKLMIRIGIFSILYT  
: \* :\*: : .:\* :: : .::: :\*: \*:

FIG. 2C

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	TM6	extracellular domain loop 3
fz3/mouse	VPLL <sup>→</sup> VVIGCYFYEQAYRGIWETTWIQERCREYHIPCPLYQVTQMS	-----RPDLILFLM
fz4/mouse	VPATCVIACYFYEISNWALFRYSADDS	-----NMAVEML
fz8/mouse	VPA <sup>→</sup> AVVACLFYEQHNRPRWEATHNCPCLRDLQPDQARR	-----PDYAVFML
fz5/human	VPASIVVACILYEQHYRESWEAALTCACPGHDTGQPRAK	-----PEYWVLM
fzd9/human	VPATCVIVCYVYERLNMDFWRLRATEQPCAAAAGPGRRDCSLP	----GGSVPTVAVFML
fzl/rat	VPATIVIACYFYEQAFRDQWERSWVAQSCSKSYAIPCPHLQGGGVPPHPPMSPDFTVFM	I
fz2/rat	VPATIVIACYFYEQAFREHWERSWVSQHCKSLAIPCPAHT	-----PRTSPDFTVYMI
fz/Dros	LPAVGLLGCLFYEYNFDEWMIQWHRDICKPFSIPCPAARAPGS	----PEARPIFOIFMV
fz2/Dros/	VPATIVIGCYLYEAAFYEDWIKALACPCAQVK--GPGKK	-----PLYSVLML
	* : . . *	::
	TM7	
fz3/mouse	KYLMALIVGIPSI <sup>→</sup> FWVGSKKTCFEWASFFHGRRKKEIVNESRQVLQEPDFAQSLLRDPNT	
fz4/mouse	KIFMSLLVGITSGMWIWSAKTLHTWQKCS	-----NRLVNSGKVK----REKRG
fz8/mouse	KYFMCLVVGITSGVWVWSGKTLESWRALC	-----TRCCWASKGAAGAGAGGSG
fz5/human	KYFMCLVVGITSGVWVWSGKTVESWRRFT	-----SRCCCRPR-----RGHK-
fzd9/human	KIFMSLVVGITSGVWVWSKTFQTWQSLC	-----YRKIAAGRARA----KACRA
fzl/rat	KYLMTLIVGITSGFWIWSGKTLSWRKFY	-----TRLTNSK-----QGETT
fz2/rat	KYLMTLIVGITSGFWIWSGKTLSWRKFY	-----TRLTNSR-----HGETT
fz/Dros	KYLC <sup>→</sup> SMLVGVTS <sup>→</sup> SVWLYSSKTMVSWRNFV	-----ERLQGEPRPT----RAQAY
fz2/Dros/	KYFMALAVGITSGVWVWSGKTLESWRRFW	-----RRLGAPDRTGANQALIKOR
	: : : * : . * : * * :	

FIG. 2D

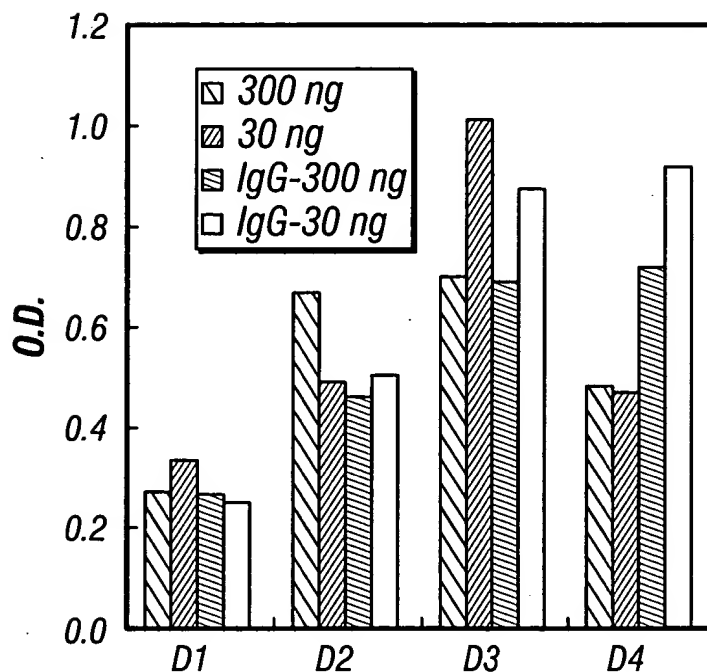
Sequence alignment of a portion of the aminoterminal extracellular region of human Frizzled receptors

HF21	VCQNTSDKGT---PSLLPEFWTSNPQHGGGCHRG	-----GFPGGAG---ASERKGFSCPR
HF22	VCQNHSEDCG-----PALLTTAPPPGLQPCAGGTPG	-----GPGGGGAPPRYATLEHPFHC
HF23	LVDLNLG-----EPTEGAPV	-----AVQRDYG-----FWC
HF24	CMEGPGD-----EE	-----VPLPHKTPI-----QP
HF25	CMDYNRSEATTAPRPPPAKPTLPG	-----PPGA-----PASGG---ECPAGGPFV-----CKC
HF26	TFDPHTEF-----LGPQKTE	-----QVQRDIG-----FWC
HF27	VCQNTSDGSGGPGGPTAYPTAPYLPDLPTALPPG	-----ASDCRGRPAF-----PFSC
HF28	CMDYNRTDLTTAAPSPPRRLP PPP-GEQPPSGSGHGRPPGARPPHGGGGGGGDAAPARGGGGGKARPPGGGAAP	---CEPGCQC
HF29	CMEAPENA-TAGPAEPHKGLGMLPV	-----APRPARPPG-----DLGP
HF210	NYLCMEAPNN-----GSDEPTRGSGLFPP	-----LFRPQRPHSAQ---EHP

FIG. 3

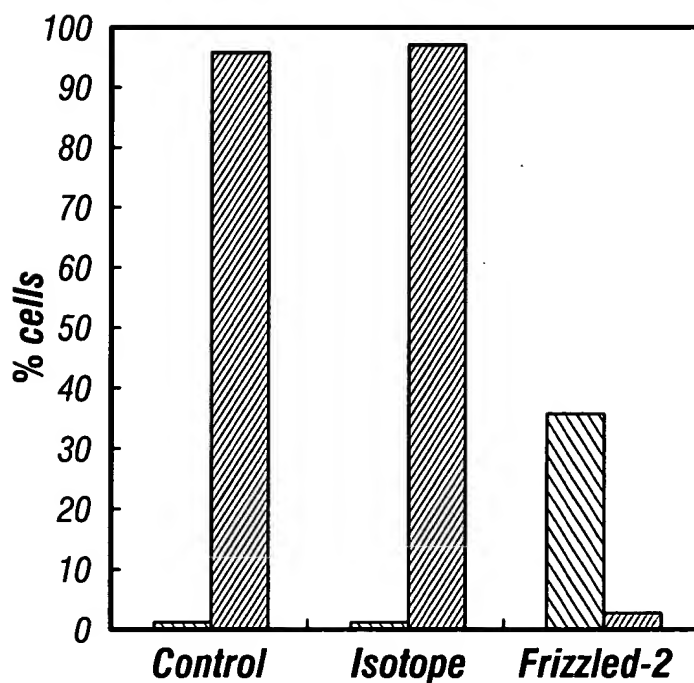
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**Effect of FZD on SNU1076 cells**



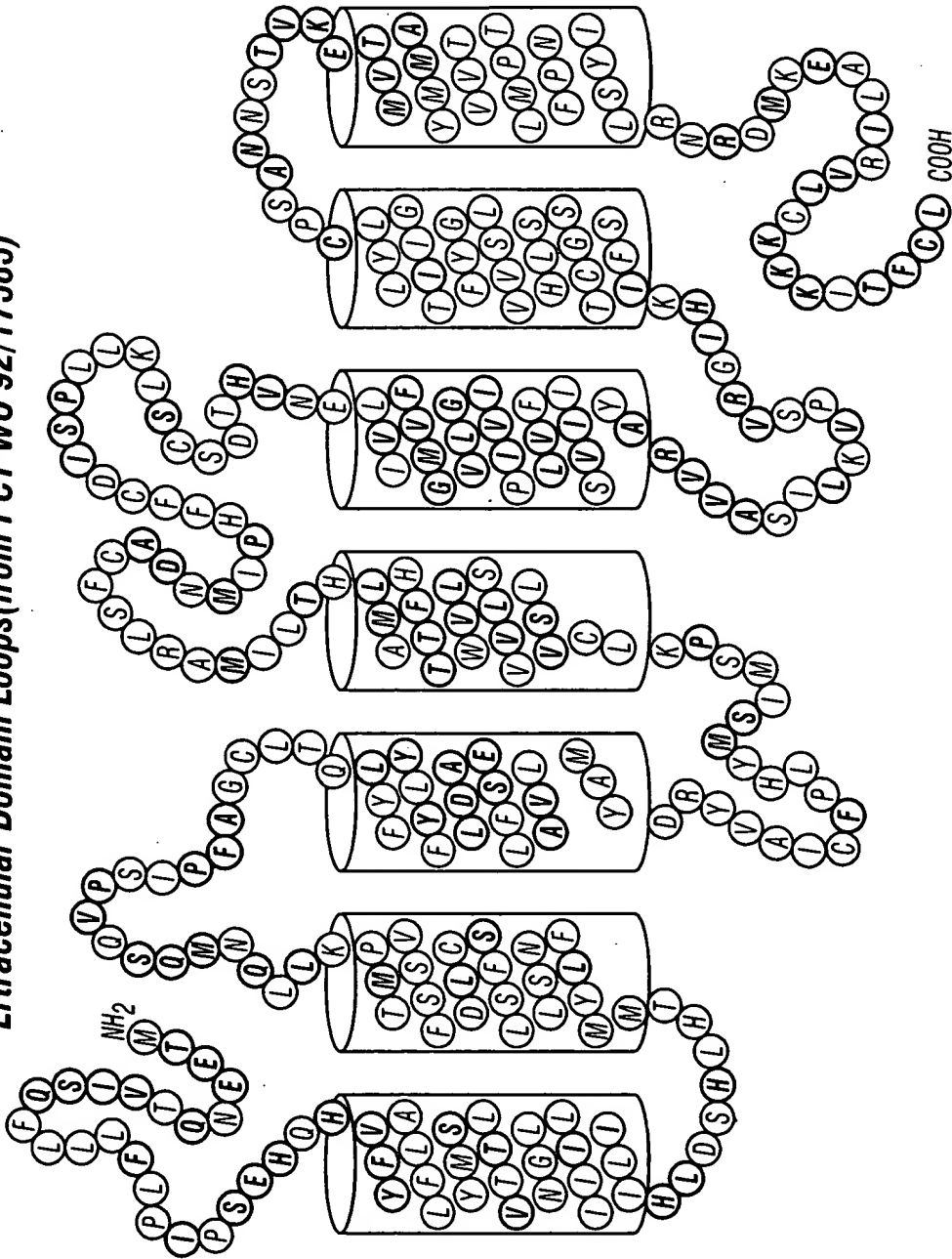
**FIG. 4**

**Effect of antibodies SNU 1076 Cells**



**FIG. 5**

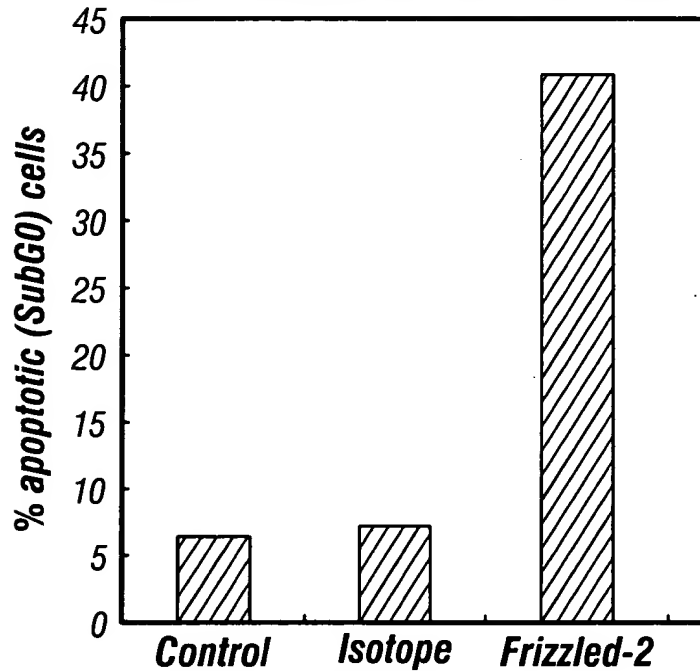
**Graphical Representation of an Olfactory Protein showing Amino-terminal and three Extracellular Domain Loops (from PCT WO 92/17585)**



**FIG. 7**

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**Effect of antibodies SNU 1076 Cells**



**FIG. 6**

→ amino terminal domain

HFZ1	MAEEEAPKKSRAAGGASWELCAGALSARLAEEGSGDAGGRRRPPVDPRRLARQLLLLLLW
MFZ1	MAEEAAPSESRAAGR-LSLELCAEALPGRREEVGHEDTASHRRPRADPRRWASGLLLLLLW
HFZ2	-----MRPRSALPRLLLPLL
HFZ3	-----MAMTWIVFSLWPLTV
MFZ3	-----MAVSWIVFDLWLLTV
HFZ4	-----MAWRGAGPSVPGAPGGVGLSLGLLLQ
MFZ4	-----MAWPGTGPPSRGAPGGVGLRLGLLLQ
HFZ5	-----MARPDPSAPPSLL--LLL
HFZ6	-----MEMFTFLLTCI
MFZ6	-----MERSPFLLACI
HFZ7	-----MRDPGAAAPLSSLGLCALVLA
MFZ7	-----MRGPGTAASHSPGLGLCALVLA
HFZ8	-----MEWGYLLEVTSLAALAL
MFZ8	-----MEWGYLLEVTSLAALAV
HFZ9	-----MAVAPL-RGALLLWQLLA
MFZ9	-----MAVPPLLRGALLLWQLLA
HFZ10	-----MQRPGPRLWLVLQ

**FIG. 8A**



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HFZ1	LLEAPLLLGVRAQAAGQPGQPGPGQPPPPPPQQQSQQYNGERGISVPDHGYCQPIS
MFZ1	LLEAPLLLGVRAQAAGQVSG---PGQQA PPPPQQSQQYNGERGISIPDHGYCQPIS
HFZ2	LLPA-----A-----GPAQFHGEKGISIPDHGFCQPIS
HFZ3	FMGHI-----GGHSLFS-----CEPIT
MFZ3	FLGQI-----GGHSLFS-----CEPIT
HFZ4	LLLLLG-----PARGFGDEEE-----RRC DPIR
MFZ4	FLLLLR-----PTLGF GDEEE-----RRC DPIR
HFZ5	LAQLVG-----RAAAASKAPV-----CQEIT
HFZ6	FLPLL-----RGHSLFT-----CEPIT
MFZ6	LLPLV-----RGHSLFT-----CEPIT
HFZ7	LLGAL-----SAGAGAPYHGEKGISVPDHGFCQPIS
MFZ7	LLGAL-----PTDTRAQPYHGEKGISVPDHGFCQPIS
HFZ8	LQRSSG-----AAAASAKELA-----CQEIT
MFZ8	LQRSSG-----AAAASAKELA-----CQEIT
HFZ9	AGGAAL-----EIGRFDPERGR---GAAPCQAVE
MFZ9	TGGAAL-----EIGRFDPERGR---GPAPCQAME
HFZ10	VMGSCA-----AISSMDMERP---GDGKCQPIE

\*:

HFZ1	IPLCTDIAYNQTIMPNNLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCT-V
MFZ1	IPLCTDMAYNQTIMPNNLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCT-V
HFZ2	IPLCTDIAYNQTIMPNNLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCT-V
HFZ3	LRMCQDLPYNTTFMPNNLNHYDQQTAAALAMEPFHPMVNLDCSRDFRPF L CALYAPICM-E
MFZ3	LRMCQDLPYNTTFMPNNLNHYDQQTAAALAMEPFHPMVNLDCSRDFRPF L CALYAPICM-E
HFZ4	ISM CQNLGYNVTKMPNLVGHELQTD AELQLTFTPLIQYGCSSQLQFFLC SVIVPMCTEK
MFZ4	IAM CQNLGYNVTKMPNLVGHELQTD AELQLTFTPLIQYGCSSQLQFFLC SVIVPMCTEK
HFZ5	VPMCRGIGYNLTHMPNQFNHDTQDEAGLEVHQFWPLVEIQ CSPDLRFFLC TMYTPICLPD
HFZ6	VPRCMK MAYNMTFFPNLMGHYDQSI AAVEMEHFLPLANLE C SPNIETFLCKAFVPTCI-E
MFZ6	VPRCMK MTYNMTFFPNLMGHYDQGI AAVEMGHFLHLANLE C SPNIEMFLCQAFIPTCT-E
HFZ7	IPLCTDIAYNQTILPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLC SMYAPVCT-V
MFZ7	IPLCTDIAYNQTILPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLC SMYAPVCT-V
HFZ8	VPLCKGIGYNYTYPNQFNHDTQDEAGLEVHQFWPLVEIQ CSPDLKFFLC SMYTPICLED
MFZ8	VPLCKGIGYNYTYPNQFNHDTQDEAGLEVHQFWPLVEIQ CSPDLKFFLC SMYTPICLED
HFZ9	IPMCRGIGYNLTRMPNNLGHTSQGEAAAE LAEFAPLVQYGC HSHLRFFLC SLYAPMCTDQ
MFZ9	IPMCRGIGYNLTRMPNNLGHTSQGEAAAE LAEFSPLVQYGC HSHLRFFLC SLYAPMCTDQ
HFZ10	IPMCKDIGYNMTRMPNLMGHENQREAAIQLHEFAPLVEYGC HSHLRFFLC SLYAPMCTEQ

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FIG. 8B

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HFZ1	LEQALPPCRSLCERARQGCEALMNKFGFQWPDTLKCEKFPVHG--AGELCVGQNTSDKGT
MFZ1	LEQALPPCRSLCERARQGCEALMNKFGFQWPDTLKCEKFPVHG--AGELCVGQNTSDKGT
HFZ2	LEQAIPPCRSICERARQGCEALMNKFGFQWPERLRCEHFPRHG--AEQICVGQNHSDEGA
HFZ3	YGRVTLPCRRLCQRAYSECSKLMEMFGVPWPEDMECSRFPDCD-EPYPRLVDLNLG---
MFZ3	YGRVTLPCRRLCQRAYSECSKLMEMFGVPWPEDMECSRFPDCD-EPYPRLVDLNLVG---
HFZ4	INIPIGPCGGMCLSVKRRCEPVLKEFGFAWPESLNCSKFPQON-DHNHMCMEGPGD----
MFZ4	INIPIGPCGGMCLSVKRRCEPVLREFGFAWPDTLNCSKFPQON-DHNHMCMEGPGD----
HFZ5	YHKPLPPCRSVCERAKAGCSPLMRQYGFAPWPERMSCDRLPVLGRDAEVLCDYNRSEATT
HFZ6	QIHVVPPCRKLCEKVYSCKKLIDTFGIRWPEELECDRLQYCD-ETVPVTFDPHTEF---
MFZ6	QIHVVLPCKRLCEKIVSDCKKLMDTFGIRWPEELCNRLPHCD-DTVPVTSHPHTEL---
HFZ7	LDQAIPPCRSICERARQGCEALMNKFGFQWPERLRCEHFVHG--AGEICVGQNTSDGSG
MFZ7	LDQAIPPCRSICERARQGCEALMNKFGFQWPERLRCEHFVHG--AGEICVGQNTSDGSG
HFZ8	YKKPLPPCRSVCERAKAGCAPLMRQYGFAPWDRMRCRLPEQG-NPDTLCMDYNRTDLTT
MFZ8	YKKPLPPCRSVCERAKAGCAPLMRQYGFAPWDRMRCRLPEQG-NPDTLCMDYNRTDLTT
HFZ9	VSTPIACRPMCEQARLRCAPIEQFNFGWPDSDLCARLPTRN-DPHALCMEAPENA-TA
MFZ9	VSTPIACRPMCEQARLRCAPIEQFNFGWPDSDLCARLPTRN-DPHALCMEAPENA-TA
HFZ10	VSTPIACRVMCEQARLKCSPIMEQFNFKWPDSDLCKLPNKN-DPNYLCMEAPNN----

. \* : \* \* : : \* : : .

HFZ1	PT---PSLLPEFWTSNPQHGGGGHRG-----
MFZ1	PT---PSLLPEFWTSNGQHGGGGYRG-----
HFZ2	-----PALLTTAPPPGLQPGAGGTPG-----
HFZ3	---EPTEGAPV-----A
MFZ3	---DPTEGAPV-----A
HFZ4	-----EE-----V
MFZ4	-----EE-----V
HFZ5	APPRPFPKPTLPG-----PPGA-----PASGG-----
HFZ6	---LGPQKKTE-----Q
MFZ6	---SGPQKKSD-----Q
HFZ7	GPGGGPTAYPTAPYLPDLPFTALPPG-----
MFZ7	GAGGSPTAYPTAPYLPDPPFTAMSP-----
HFZ8	AAPSPPRRLPPPPP-GEQPPSGSGHGRPPGARPPHRGGGRGGGGDAAAPPARGGGGGGK
MFZ8	AAPSPPRRLPPPPPGEQPPSGSGHSRPPGARPPHRGGSSRGSGDAAAPPARGG----K
HFZ9	GPAEPHKGLGMLPV-----A
MFZ9	GPTEPHKGLGMLPV-----A
HFZ10	GSDEPTRGSGLFPP-----L

FIG. 8C

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HFZ1 GFPGGAG----ASERGFSCPRALKVPSYLNHFLGEKDCGAPCEPTKVYGLMYFGPEEL  
 MFZ1 GYPGGAG----TVERGFSCPRALRVPSYLNHFLGEKDCGAPCEPTKVYGLMYFGPEEL  
 HFZ2 GPGGGGAPPRIATLEHPPHCPVLKVPSYLSYKFLGERDCAAPCEPARPDGSMFFSQEET  
 HFZ3 VQRDYG-----FWCPRELKIDPDLGYSFLHVRDCSPPCP----NMYFR--REEL  
 MFZ3 VQRDYG-----FWCPRELKIDPDLGYSFLHVRDCSPPCP----NMYFR--REEL  
 HFZ4 PLPHKTPI-----QPGEECHSVGTNSDQYIWWKRS LNCVLKCGYDAGLY--SRSAK  
 MFZ4 PLPHKTPI-----QPGEECHSVGSNSDQYIWWKRS LNCVLKCGYDAGLY--SRSAK  
 HFZ5 ECPAGGPFV-----CKCREPFVPIKESHPLYNKVRTGQVPCAVPCYOPSFSADER  
 HFZ6 VQRDIG-----FWCPRHLKTSGGQGYKFLGIDQCAPP CP----NMYFK--SDEL  
 MFZ6 VPRDIG-----FWCPKHLRTSGDQGYRFLGIEQCAPP CP----NMYFK--SDEL  
 HFZ7 ASDGRGRPAF-----PFSCPRQLKVPPYLGYRFLGERDCGAPCEPGRANGLMYFKEEER  
 MFZ7 -SDGRGRLSF-----PFSCPRQLKVPPYLGYRFLGERDCGAPCEPGRANGLMYFKEEER  
 HFZ8 ARPPGGGAAP---CEPGCQCRAPMVS VSSERHPLYNRVKTGQIANCALPCHNPFFSQDER  
 MFZ8 ARPPGGGAAP---CEPGCQCRAPMVS VSSERHPLYNRVKTGQIANCALPCHNPFFSQDER  
 HFZ9 PRPARPPG-----DLGPGAGSGTCENPEKFQYVEKSRSCAPRCGPGVEVFW SRRDK  
 MFZ9 PRPARPPG-----DSAPGPGSGGTC DNPEKFQYVEKSRSCAPRCGPGVEVFW SRRDK  
 HFZ10 FRPQRPHSAQ----EHPLKDGGPGRGGCDNPGKFHHVEKSASCAPLCTPGVDVYWSREDK

HFZ1 RFSRTWIGIWSVLCCASTLFTVLTYLVDMMRRFSYPERPIIFLSGCTAVAVAYIAGFLL E  
 MFZ1 RFSRTWIGIWSVLCCASTLFTVLTYLVDMPRFSYPERPIISLSGCTAVAVAYIAGFLL E  
 HFZ2 RFARLWILTWSVLCCASTFTTTLTYLVDMMRRFSYPERPIIFLSGCTMVSVAIYAGFVLQ  
 HFZ3 SFARYFIGLISIICLSATLFTLFTLIDVTRFRYPERPIIFYAVCYMMVSLIFFIGFLL E  
 MFZ3 SFARYFIGLISIICLSATLFTLFTLIDVTRFRYPERPIIFYAVCYMMVSLIFFIGFLL E  
 HFZ4 EFTDIWMAVWASLCFISTFTVLTFLIDSSRFSYPERPIIFLSMCYNIYSIAYIVRLTVG  
 MFZ4 EFTDIWMAVWASLCFISTFTVLTFLIDSSRFSYPERPIIFLSMCYNIYSIAYIVRLTVG  
 HFZ5 TFATFWIGLWSVLCFISTSTTVATFLIDMTFRYPERPIIFLSACYLCVSLGFLVRLVVG  
 HFZ6 EFAKSFIGTVSIFCLCATLFTLFTLIDVRRFRYPERPIIYYSVCYSIVSLMYFIGFLLG  
 MFZ6 DFAKSFIGIVSIFCLCATLFTLFTLIDVRRFRYPERPIIYYSVCYSIVSLMYFVGFLLG  
 HFZ7 RFARLWVGWWSVLCCASTLFTVLTYLFDMMRRFSYPERPIIFLSGCTFMVAVAHVAGFLL E  
 MFZ7 RFARLWVGWWSVLSASTLFTVLTYLVDMMRRFSYPERPIIFLSGCTFMVAVAHVAGFLL E  
 HFZ8 AFTVFWIGLWSVLCFVSTFATVSTFLIDMERFKYPERPIIFLSACYLFVSVGYLVRLVAG  
 MFZ8 AFTVFWIGLWSVLCFVSTFATVSTFLIDMERFKYPERPIIFLSACYLFVSVGYLVRLVAG  
 HFZ9 DFALVWMAVWSALCFFSTFTVLTFLLEPHRFQYPERPIIFLSMCYNVYSLAFLIRAVAG  
 MFZ9 DFALVWMAVWSALCFFSTFTVLTFLLEPHRFQYPERPIIFLSMCYNVYSLAFLIRAVAG  
 HFZ10 RFAVVWLAIWAVLCFFSSAFTVLTFLIDPARFRYPERPIIFLSMCYCVYSGYLIRLFAG

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FIG. 8D

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→ extracellular domain loop 1

HFZ1	DRVVCNDK-----	FAEDGARTVAQGTTK
MFZ1	DRVVCNDK-----	FAEDGARTVAQGTNK
HFZ2	ERVVCNER-----	FSEDGYRTVVQGTKK
HFZ3	DRVACNAS-----	I---PAQYKASTVTQGSNN
MFZ3	DRVACNAS-----	S---PAQYKASTVTQGSNN
HFZ4	RERISCDF-----	EEAAEPVLIQEGLN
MFZ4	RERISCDF-----	EEAAEPVLIQEGLN
HFZ5	HASVACS-----	RE-----HNHIIHETTGP
HFZ6	DSTACNKA-----	D---EKLELGDTVVLGSON
MFZ6	NSTACNKA-----	D---EKLELGDTVVLGSKN
HFZ7	DRAVCVER-----	FSDDGYRTVAQGTKK
MFZ7	DRAVCVER-----	FSDDGYRTVAQGTKK
HFZ8	HEKVACSGGAPGAGGAGGAGGAAA-GAGAAGAGAGGPGGRGEYEELGAVEQHVRVYETTGP	
MFZ8	HEKVACSGGAPGAGGAGGAGGAAAAGAGAAGRGASSPGARGEYEELGAVEQHVRVYETTGP	
HFZ9	AQSVACD-----	QEAGALYVIOEGLEN
MFZ9	AQSVACD-----	QEAGALYVIOEGLEN
HFZ10	AESIACD-----	RDSGQLYVIOEGLES

←

HFZ1	EGCTILEMMLYFFSMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHAAWAVPAIKT
MFZ1	EGCTILEMMLYFFSMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHAAWAVPAIKT
HFZ2	EGCTILEMMLYFFSMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHAAWAVPAVKT
HFZ3	KACTMLEMILYFFTMAGSVWWVILTITWFLAAVPKWGSEAIEKKALLFHASAWGIPGTLT
MFZ3	KACTMLEMVLFFTMAGSVWWVILTITWFLAAVPKWGSEAIEKKALLFHASAWGIPGTLT
HFZ4	TGCAIIFLLMYFFGMASSIWWVILTLTWFLAAGLKWGHEAIEMHSSYFHIAAWAIPAVKT
MFZ4	TGCAIIFLLMYFFGMASSIWWVILTLTWFLAAGLKWGHEAIEMHSSYFHIAAWAIPAVKT
HFZ5	ALCTIVFLLVYFFGMASSIWWVILSLTWFLAAGMKWGNEAIEAGYQYFHAAWLVPSVKS
HFZ6	KACTVLFMLLYFFTMAGTVWWVILTITWFLAAGRKWSCEAIEQKAVWFHAVAWGTPGFLT
MFZ6	KACSVFMFLYFFTMAGTVWWVILTITWFLAAGRKWSCEAIEQKAVWFHAVAWGAPGFLT
HFZ7	EGCTILEMVLFFGMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHAAWAVPAVKT
MFZ7	EGCTILEMVLFFGMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHAAWAVPAVKT
HFZ8	ALCTVFLVLYFFGMASSIWWVILSLTWFLAAGMKWGNEAIEAGYSQYFHAAWLVPSVKS
MFZ8	ALCTVFLVLYFFGMASSIWWVILSLTWFLAAGMKWGNEAIEAGYSQYFHAAWLVPSVKS
HFZ9	TGCTLVFLLLYFFGMASLWVVLTLTWFLAAGKKWGHEAIEAHGSYFHMAAWGLPALKT
MFZ9	TGCTLVFLLLYFFGMASLWVVLTLTWFLAAGKKWGHEAIEAHGSYFHMAAWGLPALKT
HFZ10	TGCTLVFLVLYFFGMASLWVVLTLTWFLAAGKKWGHEAIEANSYFHAAWAVPAVKT

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FIG. 8E

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↪ extracellular domain loop 2 ◀

HFZ1	ITILALGQVDGDLVSGVCFVGLNNVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
MFZ1	ITILALGQVDGDLVSGVCFGLNNVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
HFZ2	ITILAMGQIDGDLVSGVCFVGLNSLDPLRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
HFZ3	IILLAMNKIEGDNISGVCFVGLYDVALRYFVLAPLCYVVVGVSLLLAGIISLNRVRIE
MFZ3	IILLAMNKIEGDNISGVCFVGLYDVALRYFVLAPLCYVVVGVSLLLAGIISLNRVRIE
HFZ4	IVILIMRLVDADELTGLCYVGNQNLDAITGFVAPLFTYLVIGTLFIAAGLVALEFKIRSN
MFZ4	IVILIMRLVDADELTGLCYVGNQNLDAITGFVAPLFTYLVIGTLFIAAGLVALEFKIRSN
HFZ5	ITALALSSVDGDPVAGICYVGNQNLNLRRLVGLPLVLYLLVGTFLFLLAGFVSLFRIRSV
HFZ6	VMLLAMNKVEGDNISGVCFVGLYDLASRYFVLLPLCLCVFVGLSLLLAGIISLNHVRQV
MFZ6	VMLLAMNKVEGDNISGVCFVGLYDLASRYFVLLPLCLCVFVGLSLLLAGIISLNHVRQV
HFZ7	ITILAMGQVDGDLVSGVCFVGLSSVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
MFZ7	ITILAMGQVDGDLVSGVCFVGLSSVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
HFZ8	IAVLALSSVDGDPVAGICYVGNQSLDNLRGFVLAPLVIYLFIGTMFLLAGFVSLFRIRSV
MFZ8	IAVLALSSVDGDPVAGICYVGNQSLDNLRGFVLAPLVIYLFIGTMFLLAGFVSLFRIRSV
HFZ9	IVILTLRKVAGDELTGLCYVASTDAAALTGFVLVPLSGYLVLGSSFLTGFVALFHIRKI
MFZ9	IVVLTLRKVAGDELTGLCYVASMDDPAALTGFVLVPLSCYLVLGTSFLTGFVALFHIRKI
HFZ10	ILILVMRRVAGDELTGVCYVGSMDVNALTGFVLIPLACYLVIGTSFILSGFVALFHIRRV
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↪ extracellular domain loop 3

HFZ1	MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVIACYFYEQAFRDQWERSWVAQSCKSY
MFZ1	MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVIACYFYEQAFRDQWERSWVAQSCKSY
HFZ2	MKH--DGTKTEKLERLMVRIGVFSVLYTVPATIVIACYFYEQAFREHWERSWVSQHCKSL
HFZ3	IPL--EKENQDKLVKFMIRIGVFSILYLVPLLVVIGCYFYEQAYRGIWETTIIQERCREY
MFZ3	IPL--EKENQDKLVKFMIRIGVFSILYLVPLLVVIGCYFYEQAYRGIWETTIIQERCREY
HFZ4	LQK--DGTKTDKLERLMVKIGVFSVLYTVPATCVIACYFYEQAFREHWERSWVSQHCKSL
MFZ4	LQK--DGTKTDKLERLMVKIGVFSVLYTVPATCVIACYFYEQAFREHWERSWVSQHCKSL
HFZ5	IKQ--GGTKTDKLEKLMIRIGIFTLLYTPASIVVACYLYEQHYRESWEAALTCACPGHD
HFZ6	IQH--DGRNQEKLLKFMIRIGVFSGLYLVPLVTLGCVVYEQVNRITWEITWVSDHCRQY
MFZ6	IQH--DGRNQEKLLKFMIRIGVFSGLYLVPLVTLGCVVYELVNRTWEMTWFSDHCHQY
HFZ7	MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVLACYFYEQAFREHWERTWLLQTCKSY
MFZ7	MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVLACYFYEQAFREHWERTWLLQTCKSY
HFZ8	IKQQDGPTKTHKLEKLMIRGLFTVLYTPAAVVVACLFYEQHNRPRWEATHNCPCLRDL
MFZ8	IKQQGGPTKTHKLEKLMIRGLFTVLYTPAAVVVACLFYEQHNRPRWEATHNCPCLRDL
HFZ9	MKT--GGTNTKLEKLMVKIGVFSILYTPATCVIVCYVYERLNMDFWRLRATEQPCTAA
MFZ9	MKT--GGTNTKLEKLMVKIGVFSILYTPATCVIVCYVYERLNMDFWRLRATEQPCTAA
HFZ10	MKT--GGENTDKLEKLMVRIGLFSVLYTVPATCVIACYFXEHLNMDYWKILAAQHKCKM-
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FIG. 8F

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HFZ1 AIPCPHLQAGGGAPPHPPMSPDFTVFMIKYLMTLIVGITS GFVIWSGKTLNSWRKFYTRL  
 MFZ1 AIPCPHLQGGGVPPHPPMSPDFTVFMIKYMT-----LNSWRKFYTRL  
 HFZ2 AIPCP-----AHYTPR--MSPDFTVYMIKYLMTLIVGITS GFVIWSGKTLHSWRKFYTRL  
 HFZ3 HIPCP-----YQVTQMSRPDLILFLMKYLMALIVGIPSVFVWGSKKTCEWASFFHGR  
 MFZ3 HIPCP-----YQVTQMSRPDLILFLMKYLMALIVGIPSI FVWGSKKTCEWASFFHGR  
 HFZ4 -----EMLKIFMSLLVGITSGMWIWSAKTLHTWQ-KCSNR  
 MFZ4 -----EMLKIFMSLLVGITSGMWIWSAKTLHTWQ-KCSNR  
 HFZ5 TGQPR---AK-----PEYWVLMKYFMCLVVGITSGVWIWSGKTVESWRRFTSRC  
 HFZ6 HIPCP-----YQAKAKARPELALFMIKYLMTLIVGISAVFVWGSKKTCTEWAGFFKRN  
 MFZ6 RIPCP-----YQANPKARPELALFMIKYLMTLIVGISAVFVWGSKKTCTEWAGFFKRN  
 HFZ7 AVPCP---PGHFPPM---SPDFTVFMIKYLMTMIVGITTGFVIWSGKTLQSWRRFYHRL  
 MFZ7 AVPCP---PRHFSPM---SPDFTVFMIKYLMTMIVGITTGFVIWSGKTLQSWRRFYHRL  
 HFZ8 QPDQA---RR-----PDYAVFMLKYFMCLVVGITSGVWVWSGKTLESWRS LCTRC  
 MFZ8 QPDQA---RR-----PDYAVFMLKYFMCLVVGITSGVWVWSGKTLESW RALCTRC  
 HFZ9 AGPGG---RRDCSLPGGSVPTVAVFMLKIFMSLVVGITSGVWVWS SKTFTQWQSLCYRK  
 MFZ9 TVPGG---RRDCSLPGGSVPTVAVFMLKIFMSLVVGITSGVWVWS SKTFTQWQSLCYRK  
 HFZ10 NNQTK---TLDC-LMAASIPAVEIFMVKIFMLLVVGITSGMWI WTSKTLQSWQVCSRR

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HFZ1 TN--SKQGETTV-----  
 MFZ1 TN--SKQGETTV-----  
 HFZ2 TN--SRHGETTV-----  
 HFZ3 RKKEIVNESRQVLQEP-----DFAQSLLRDPNTPIIRKSRGTSTQGTSTHAS  
 MFZ3 RKKEIVNESRQVLQEP-----DFAQSLLRDPNTPIIRKSRGTSTQGTSTHAS  
 HFZ4 LVNSGKVKREKRGNGW-----VKPGKGSE-----  
 MFZ4 LVNSGKVKREKRGNGW-----VKPGKGNE-----  
 HFZ5 CC-RPRRGHKSGGA-----MA--AG-D-----  
 HFZ6 RKRDPISERRLVQESCEFFLKHNSKVKKKKHYKPSSHLKVISKSMGTSTGATANHGT  
 MFZ6 RKRDPISERRLVQESCEFFLKHNSKVKKKKHGAPGPHRLKVISKSMGTSTGATTNHGT  
 HFZ7 SH--SSKGETAV-----  
 MFZ7 SH--SSKGETAV-----  
 HFZ8 CW-ASKGA AVGGGAGA-----TAAGGGGGPGGGGGGP  
 MFZ8 CW-ASKGA AVGAGAGG-----SGPGGSGP-----GP  
 HFZ9 IA--AGRARAKACRAP-----GSYGRGTHC-----  
 MFZ9 MA--AGRARAKACRTP-----GGYGRGTHC-----  
 HFZ10 LKKKSRRKPASVITSG-----GIYKKAQH-----

FIG. 8G

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HFZ1	-----
MFZ1	-----
HFZ2	-----
HFZ3	STQLAMVDDQRSKAGSIHVKSSYHGSLHRSRDGRYTPCSYRG--MEERLPHGMS-RLT
MFZ3	STQLAMVDDQRSKAGSVHVKSSYHGSLHRSRDGRYTPCSYRG--MEERLPHGMS-RLT
HFZ4	-----TVV-----
MFZ4	-----TVV-----
HFZ5	-----YPEASAALTGRGTGPPGPAATYHKQVSLSHV-----
HFZ6	SAVAITSHDYLQETLTIQTSPETSMREVKADGASTPRLREQDCGEPASPAASIS-RLS
MFZ6	SAMAIADHDYLQETSTEVTSPASVKEGRADRANTPSAKDRDCGESAGPSSKLSGNRN
HFZ7	-----
MFZ7	-----
HFZ8	GGGGGPGGGGSLYSDVSTGLTWRSGTAS-SVSYPKQMPLSQV-----
MFZ8	GGGGHGGGGSLYSDVSTGLTWRSGTAS-SVSYPKQMPLSQV-----
HFZ9	-----H---YKAPTIVLHMTKTDPSLENPTL-----
MFZ9	-----H---YKAPTIVLHMTKTDPSLENPTL-----
HFZ10	-----PQKT-HHGKYEIPAQSPTCV-----

HFZ1	-----
MFZ1	-----
HFZ2	-----
HFZ3	DHSRHSSSHRLNEQSRHSSIRDLNPNMTHITHGTSMNRVIEEDGTS-----
MFZ3	DHSRHSSSHRLNEQSRHSSIRDLNPNMTHITHGTSMNRVIEEDGTS-----
HFZ4	-----
MFZ4	-----
HFZ5	-----
HFZ6	GEQVDGKG--QAGSVSESARSEGRISPKSDITDTGLAQSNLQVPSSSEPSSLKGSTSL
MFZ6	GRESRAGGLKERSNGSEGAPSEGRVSPKSSVPETGLIDCSTSQAAASSPEPTSLKGSTSLP
HFZ7	-----
MFZ7	-----
HFZ8	-----
MFZ8	-----
HFZ9	-----
MFZ9	-----
HFZ10	-----

FIG. 8H

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HFZ1	-----
MFZ1	-----
HFZ2	-----
HFZ3	-----
MFZ3	-----
HFZ4	-----
MFZ4	-----
HFZ5	-----
HFZ6	VHPVSGVRKEQGGGCHSDT
MFZ6	VHSASRARKEQGAGSHSDA
HFZ7	-----
MFZ7	-----
HFZ8	-----
MFZ8	-----
HFZ9	-----

**FIG. 8I**